Effect of an Investigational Vaccine for Preventing *Staphylococcus aureus* Infections After Cardiothoracic Surgery

A Randomized Trial

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**Importance** Infections due to *Staphylococcus aureus* are serious complications of cardiothoracic surgery. A novel vaccine candidate (V710) containing the highly conserved *S. aureus* iron surface determinant B is immunogenic and generally well tolerated in volunteers.

**Objective** To evaluate the efficacy and safety of preoperative vaccination in preventing serious postoperative *S. aureus* infection in patients undergoing cardiothoracic surgery.

**Design, Setting, and Participants** Double-blind, randomized, event-driven trial conducted between December 2007 and August 2011 among 8031 patients aged 18 years or older who were scheduled for full median sternotomy within 14 to 60 days of vaccination at 165 sites in 26 countries.

**Intervention** Participants were randomly assigned to receive a single 0.5-mL intramuscular injection of either V710 vaccine, 60 μg (n = 4015), or placebo (n = 4016).

**Main Outcome Measures** The primary efficacy end point was prevention of *S. aureus* bacteremia and/or deep sternal wound infection (including mediastinitis) through postoperative day 90. Secondary end points included all *S. aureus* surgical site and invasive infections through postoperative day 90. Three interim analyses with futility assessments were planned.

**Results** The independent data monitoring committee recommended termination of the study after the second interim analysis because of safety concerns and low efficacy. At the end of the study, the V710 vaccine was not significantly more efficacious than placebo in preventing either the primary end points (22/3528 V710 vaccine recipients [2.6 per 100 person-years] vs 27/3517 placebo recipients [3.2 per 100 person-years]; relative risk, 0.81; 95% CI, 0.44-1.48; P = .20) were not statistically different between groups, the mortality rate in patients with serious adverse events, respectively) and a significantly higher rate of multigran failure during the entire study (31 vs 17 events; 0.9 [95% CI, 0.6-1.2] vs 0.5 [95% CI, 0.3-0.8] events per 100 person-years; difference, 0.4 per 100 person-years; difference, 0.8 [95% CI, 0.8-1.8]).

**Conclusions and Relevance** Among patients undergoing cardiothoracic surgery with median sternotomy, the use of a vaccine against *S. aureus* compared with placebo did not reduce the rate of serious postoperative *S. aureus* infections and was associated with increased mortality among patients who developed *S. aureus* infections. These findings do not support the use of the V710 vaccine for patients undergoing surgical interventions.

**Trial Registration** clinicaltrials.gov Identifier: NCT00518687

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punts. Elevated antibody responses persisted for at least 1 year after vaccination in most patients. The immunogenicity and tolerability of a lyophilized V710 formulation were generally similar to the properties of the original liquid formulation.

The current phase 2b/3 study was initiated to evaluate the efficacy and safety of preoperative vaccination with nonadjuvanted lyophilized V710 in preventing serious S. aureus infections in patients about to undergo a median sternotomy for cardiothoracic surgery.

**METHODS**

**Objectives**

The primary efficacy objective was to demonstrate whether a single dose of V710 vaccine administered between 14 and 60 days prior to cardiothoracic surgery (involving a full median sternotomy) would reduce the proportion of adult patients with postoperative S. aureus bacteremia and/or S. aureus deep sternal wound infections through postoperative day 90 by at least 20% relative to placebo. Secondary efficacy objectives included demonstrating a reduction in the proportion of patients who developed any invasive or surgical site infection with S. aureus through postoperative day 90. The primary safety objective was to evaluate the adverse event profile of a single dose of V710 vaccine administered preoperatively to patients awaiting cardiothoracic surgery. Immunogenicity was also assessed.

**Study Design**

A sequential-design, multicenter, randomized, double-blind, placebo-controlled trial was conducted internationally to evaluate the safety, efficacy, and immunogenicity of a 60-µg dose of V710 vaccine in patients aged 18 years or older scheduled for cardiothoracic surgery involving a full median sternotomy within 14 to 60 days following vaccination. The protocol was approved by the institutional review boards or ethical review committees at each site and executed in accordance with Good Clinical Practice guidelines. Patients were excluded if pregnant or breastfeeding, febrile (\(\geq 38.0^\circ\text{C} [100.4^\circ\text{F}]\)) in the previous 48 hours, immunocompromised (including but not limited to human immunodeficiency virus infection or immunosuppressive therapies), unstable, or recently immunized with any other vaccine (except for pneumococcal or influenza vaccines, which were allowed at least 7 days prior to or 15 days after study vaccination). Patients with cirrhosis, bleeding diathesis, renal failure requiring dialysis, or a history of injecting recreational drugs in the last 5 years were also excluded. At screening, specific preoperative variables were assessed to calculate a Society of Thoracic Surgeons score for the risk of major infections following cardiothoracic surgery with higher scores representing greater risk. Eligible patients provided written informed consent before any study procedures took place.

The V710 vaccine was provided as a lyophilized formulation without adjuvant stored at 2°C to 8°C (35.6°F to 46.4°F). The 0.45% saline diluent for V710 reconstitution and the placebo solution were kept at room temperature. The vaccine was to be reconstituted immediately before use, resulting in a clear, colorless to slightly yellow liquid, and administered by an unblinded pharmacist or study coordinator not otherwise involved in the patient’s subsequent care.

Participants were randomized in a 1:1 ratio (Figure) by site using an interactive voice response system to receive a single 0.5-mL injection of either 60 µg of V710 vaccine or 0.9% saline placebo in the deltoid (or thigh) muscle at the time of enrollment. Patients were monitored for evidence of immediate hypersensitivity reactions for 30 minutes after vaccination. The total time in the study for each patient was to be 14 to 60 days from vaccination to cardiothoracic surgery and another 360 days postoperatively; after termination of enrollment, patients still in the study were followed up for at least 90 days after vaccination. Study patients were mandated to receive preoperative antibiotic prophylaxis in addition to other customary preoperative and perioperative measures according to the local standard of care. The protocol offered nonbinding recommendations regarding selection, timing, and duration of prophylactic antibiotics. An independent data monitoring committee reviewed safety data on an ongoing basis and in conjunction with the predefined interim efficacy analyses.

**Case Definitions and Adjudication Process**

All efficacy end points were assessed through postoperative day 90 and adjudicated by an independent adjudication committee blinded to treatment group using the Centers for Disease Control and Prevention’s definitions for nosocomial infections. For the primary end points, bloodstream infection was defined as at least 1 positive blood culture for S. aureus (regardless of the presence of clinical symptoms) and deep sternal wound infection was defined as postoperative mediastinitis or a surgical site infection involving the sternum or deeper myofascial tissue planes. The secondary efficacy end points were invasive S. aureus infections (including bacteremia or any deep-seated infection) and superficial or deep surgical site infections (including the sternotomy, vascular harvest, and chest tube sites).

**Statistical Analysis**

The study was designed to detect at least a 20% reduction in the number of cases based on the prespecified combined end point of S. aureus bacteremia and/or S. aureus deep sternal wound infections through postoperative day 90 in V710 recipients compared with placebo recipients (ie, vaccine efficacy >20%). All reported adverse events irrespective of intensity or causality were tabulated for the 14-day period immediately following vaccination; selected serious adverse events continued to be collected for the entire 360-day postoperative length of the study. Patients were
handled as randomized for the primary efficacy analysis and as treated for the safety analysis.

The trial was event-driven, using the number of S aureus cases rather than number of enrolled patients for measuring trial progress and defining when the trial was complete. Total enrollment was estimated from the expected number of accumulated cases of S aureus bacteremia and/or S aureus deep sternal wound infections. A group-sequential design with 4 distinct stages (at 24, 48, 77, and 107 primary end point events) was used in the study such that after each threshold of primary end point events was reached, an analysis of futility and/or efficacy was conducted. Group-sequential methods using exact methods for binomial data (which adjusted for the predefined success and futility stopping rules at each stage) were used to calculate the exact power, type I error rate, and confidence intervals for efficacy. Stopping rules for futility were chosen to ensure that the probability of moving forward with a nonefficacious vaccine would be low while controlling the 1-sided type I error rate at 2.5%. Additionally, the stopping rules for success were selected such that if they were met, the resulting lower limit of the con-
idence interval for vaccine efficacy would be greater than 20% (the predefined threshold for study success). Only futility was assessed at the first 2 stages to guarantee that a sufficiently large safety database would be collected prior to potentially stopping for success.

The initial interim review after 24 primary end point events had been accrued was to serve as a safety assessment and futility analysis; the study was to be terminated early if at least 13 *S aureus* cases (of the 24 total cases) occurred in the V710 vaccine group. The second interim analysis, planned once 48 cases had been accrued, was also intended to assess futility, defined as at least 22 cases in the V710 group. The third interim analysis was to include 77 cases to assess both futility and efficacy. Futility was to be declared at the last interim analysis if at least 32 cases occurred in the V710 group. The statistical criterion for success was specified as the lower bound of the exact 95% confidence interval for vaccine efficacy greater than 20% and would be met at this interim analysis if 22 or fewer cases occurred in the V710 group.

If criteria for futility or success were not satisfied during the interim analyses, the trial was to continue enrollment until the final target of 107 *S aureus* cases had been accrued. With 107 cases, an assumed vaccine efficacy of 60%, and a type I error of .05, the study had an overall power of approximately 92% to conclude that the true vaccine efficacy was greater than 20%. An estimated 15,000 patients would be required to accrue the 107 *S aureus* cases necessary for the final analysis. A lower bound of the exact 95% confidence interval for efficacy of V710 relative to placebo of greater than 20% for the primary combined end point would establish that the vaccine was efficacious as predefined by protocol. If the primary hypothesis was satisfied, a vaccine efficacy greater than 0% against a secondary end point would allow the further conclusion that the vaccine was efficacious in preventing the particular end point.

### Efficacy Analyses

**Study efficacy results were based on a modified intention-to-treat (ITT) approach.** Vaccine efficacy was defined by protocol as the relative risk reduction of an end point in vaccine recipients compared with the placebo group. The primary efficacy analysis was conducted in the primary modified ITT population, prespecified as vaccinated patients who underwent full median sternotomy between day 14 and day 60 after vaccination and who did not develop a serious preoperative *S aureus* infection. The primary modified ITT population was denoted as the full analysis set in the protocol. The primary efficacy analysis was supported by a secondary modified ITT analysis and a per-protocol analysis. A secondary modified ITT population included vaccinated patients who subsequently underwent cardiothoracic surgery irrespective of the type of surgical procedure or timing relative to vaccination. Patients who developed serious preoperative *S aureus* infections were retained in the secondary modified ITT population. The per-protocol population included vaccinated patients undergoing full median sternotomy between day 14 and day 60 after vaccination with neither serious preoperative *S aureus* infections nor major protocol violations. Cross-treated patients were analyzed based on the vaccination group to which they were randomized in the primary and secondary modified ITT populations and based on what they actually received in the per-protocol population.

To supplement the estimates of vaccine efficacy stipulated in the protocol and required by regulatory agencies (which were based on the case split without regard to duration of follow-up), relative risks (which accounted for both the number of patients and length of follow-up time) were calculated for the key primary efficacy results.

### Safety Analyses

All vaccinated patients with follow-up data were included in the adverse experiences summaries as treated. Adverse experiences reported by the site investigator as possibly, probably, or definitely vaccine-related were tallied as vaccine-related. Injection site reactions and oral temperatures were actively monitored for 5 days after vaccination. All adverse experiences in the 14 days immediately after vaccination were captured using a patient vaccine report card. Serious adverse experiences considered to be vaccine-related, associated with *S aureus* infection, and/or resulting in death were to be reported throughout the entire study. Subsequent to recognition of a safety signal, the incidence of multiorgan failure was retrospectively assessed irrespective of causality or timing. Diagnoses of “multiorgan failure” were accepted verbatim as an adverse event term reported by the site investigators; no definitions or criteria were imposed per protocol because this complication was not anticipated as an issue a priori. Extensive post hoc exploratory analyses were performed to investigate safety concerns. After the decision to terminate the study was made, all vaccinated patients still in the study were to be followed up at least until postvaccination day 90. Due to the potential for differing follow-up times for individual patients, the overall adverse event rate was to be expressed as the number of patients with adverse experiences per 100 person-years of follow-up. Patients developing multiple adverse experiences were counted only once in any given category.

Prior to the early study termination, the primary safety end point had been specified per protocol as the incidence of vaccine-related serious adverse experiences developing at any time after vaccination through postoperative day 180. The point estimate with its corresponding 2-tailed 95% confidence interval for the risk difference between the V710 and placebo groups of developing a vaccine-related serious adverse experience was to be calculated using the method of Miettinen and Nurminen for analysis of Poisson rates accounting for the potential differential follow-up time. Frequencies were also
computed for adverse experiences occurring during the 14-day postvaccination period.

Immunogenicity Analyses

Blood samples were to be collected from all patients just before vaccination, at the time of hospitalization for surgery (14 to 60 days after vaccination), and on postoperative days 45 and 90 for exploratory immunogenicity analyses. In a preselected subset of patients, additional specimens were to be obtained on postoperative days 180, 270, and 360 as well. A direct binding assay was developed for the detection of total IgG antibodies to the iron surface determinant of S. aureus using a Luminox platform. Opsonophagocytic activity was assessed with an investigational assay by the uptake of fluorescently labeled S. aureus by a human granulocytic cell line in the presence or absence of patient serum, comparing postvaccination to preimmune serum samples.

RESULTS

Patient Accounting and Baseline Characteristics

The study was conducted from December 12, 2007, to August 19, 2011, at 165 sites in 26 countries on 5 continents. No concerns were raised by the data monitoring committee following the initial interim analysis in January 2010. Following the second interim analysis on April 8, 2011, the data monitoring committee recommended suspension of enrollment and vaccination because of concerns about a possibly higher rate of mortality and multiorgan failure in V710 vaccine recipients than in placebo recipients, and the committee requested further analyses. On June 2, 2011, following review of the supplemental results, the data monitoring committee recommended permanently closing the study to enrollment because of continuing safety concerns coupled with the low probability of success. The sponsor followed the recommendations from the data monitoring committee.

When the database was locked on September 13, 2011, 7983 participants had been vaccinated (Figure). Because repeated audits had uncovered irregularities in clinical practices at 1 site, 21 patients from this site were excluded from all analyses before the data were unblinded. Five participants were inadvertently given the wrong injection based on the group to which they had been randomized. Two patients in each group experienced a serious preoperative S. aureus infection leading to exclusion from the primary efficacy population; none of these 4 patients developed a postoperative S. aureus infection. Approximately 64% of patients in each study group completed the 360-day safety follow-up. The predominant reason for patients discontinuing the study was the premature study termination by the sponsor in response to the recommendation of the data monitoring committee, accounting for 1848 (65%) of the total 2857 discontinuations.

Baseline characteristics of randomized patients were balanced across groups (Table 1). Vaccine and placebo recipients had similar metabolic characteristics, infection risk scores, S. aureus colonization rates, and types of surgical procedure.

Efficacy

In the primary modified ITT analysis, V710 vaccine was not significantly more efficacious than placebo in preventing the prespecified combined end point (22 adjudicated cases in 3528 evaluable V710 recipients vs 27 adjudicated cases in 3517 evaluable placebo recipients; event rate, 2.6 [95% CI, 1.6-4.0] vs 3.2 [95% CI, 2.1-4.7] per 100 person-years, respectively), yielding a relative risk of 0.81 (95% CI, 0.44-1.48). There was no significant vaccine efficacy (18.5%; 95% CI, −48.6% to 55.8%) (Table 2). No significant differences in efficacy between the vaccine and placebo groups were observed at any point during the study (eFigure 1; available at http://www.jama.com). An additional adjudicated case of S. aureus infection in a V710 vaccine recipient had been excluded from the primary analysis because it had been determined during a quality-assurance audit that the site might have used questionable clinical practices. Inclusion of this additional adjudicated case yielded a nonsignificant vaccine efficacy of 14.8% (95% CI, −54.3% to 53.3%). Two cases from each group were reported after termination of the trial and consequently not adjudicated. Counting all cases, overall vaccine efficacy with respect to the primary end point was also nonsignificant (13.8%; 95% CI, −52.5% to 51.6%).

In the secondary modified ITT analysis, estimates based on adjudicated cases ranged from 12.9% (95% CI, −50.8% to 50.0%) for preventing invasive S. aureus infections to 29.3% (95% CI, −1.8% to 51.2%) for preventing S. aureus surgical site infections. The lower number of S. aureus surgical site infections was driven by fewer superficial lower extremity (usually saphenous vein) donor site infections (13 vs 36 in the V710 and placebo groups, respectively) without a meaningful between-group difference in the infection rate for sternal wounds. However, harvesting techniques, perioperative antibiotic prophylaxis, and other adjunctive measures were not controlled and varied among sites. Combining all end points, vaccine efficacy was 25.3% (95% CI, −3.4% to 46.2%) (eFigure 2).

In a post hoc analysis, estimates of vaccine efficacy were higher in preventing methicillin-susceptible S. aureus (MSSA) than methicillin-resistant S. aureus (MRSA) infections for the primary, secondary, and exploratory end points. Infection with MRSA occurred in 23 (34%; 95% CI, 23%-46%) of the 68 V710 vaccine recipients with S. aureus infection and in 17 (19%; 95% CI, 11%-28%) of the 91 placebo recipients with S. aureus infection in the primary efficacy population (P=.04). *Staphylococcus aureus* infections developed in 3.3% (95% CI, 2.1%-4.9%) and 5.5% (95% CI, 3.9%-7.6%) of nasal carriers compared with 1.6% (95% CI, 1.2%-2.2%) and 1.8% (95% CI, 1.4%-2.4%) of noncarriers in the V710 and placebo groups, respectively (P=.09).
Safety
The V710 vaccine was associated with a higher rate of overall adverse experiences during the 14 days following vaccination, predominantly but not exclusively at the injection site (Table 3). In this immediate 14-day postvaccination period, vaccine-related injection site adverse reactions were significantly more common among V710 recipients than placebo recipients (19.2% [95% CI, 18.0%-20.5%] vs 9.1% [95% CI, 8.2%-10.0%]; difference, 10.1% [95% CI, 8.6%-11.7%]), whereas rates of vaccine-related systemic adverse experiences (3.1% [95% CI, 2.6%-3.4%]; difference, 0.3% [95% CI, −0.5% to 1.0%]), serious adverse experiences (1.7% [95% CI, 1.3%-2.1%]; difference, 0.4% [95% CI, −0.2% to 0.9%]), serious vaccine-related adverse experiences (0 events in each group), and preoperative deaths (11 deaths [0.3%; 95% CI, 0.1%-0.5%] vs 6 deaths [0.2%; 95% CI, 0.1%-0.3%]; difference, 0.1% [95% CI, −0.1% to 0.4%]) did not differ significantly between vaccine and placebo recipients, respectively.

Over the course of the entire study, 1 vaccine-related serious adverse event was reported in each group: Clostridium difficile colitis in a V710 vaccine recipient on postvaccination day 237 (postoperative day 37) and leukocytosis in a placebo recipient on postvaccination day 53 (postoperative day 222) (Table 3). No statistically significant differences in overall vaccine-related serious adverse events or all-cause mortality were found between the V710 and placebo groups, whereas postoperative multiorgan failure developed more commonly in V710 recipients than placebo recipients (31 vs 17 events, yielding 0.9 [95% CI, 0.6-1.2] vs 0.5 [95% CI, 0.3-0.8] events per 100 person-years, respectively; difference, 0.4 [95% CI, 0.0-0.8] events per 100 person-years; P = .04). In no cases were multiorgan failure or death attributed to the vaccine by the site investigator, although the placebo recipient with “vaccine-related” lymphoma later died.

All patients with reported multiorgan failure died. A full list of all serious adverse experiences in both V710 and placebo recipients is provided in the eTable. Significantly more patients with postoperative Staphylococcus aureus infections died in the V710 vaccine group (15 deaths) than in the placebo group (4 deaths), yielding respective mortality rates of 23.0

<table>
<thead>
<tr>
<th>Table 1. Selected Baseline Characteristics of Randomized Patients by Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Self-identified race</strong></td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Multiracial</td>
</tr>
<tr>
<td>Other or unknown</td>
</tr>
<tr>
<td><strong>Self-reported ethnicity</strong></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
</tr>
<tr>
<td><strong>Region</strong></td>
</tr>
<tr>
<td>Asia/Pacific (New Zealand)</td>
</tr>
<tr>
<td>Europe (including Russia)</td>
</tr>
<tr>
<td>Latin America</td>
</tr>
<tr>
<td>United States</td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td>Median (range), y</td>
</tr>
<tr>
<td>&gt;70 y</td>
</tr>
<tr>
<td><strong>Underlying metabolic conditions</strong></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>BMI &gt;30</td>
</tr>
<tr>
<td>Society of Thoracic Surgeons infection risk score, median (range)</td>
</tr>
<tr>
<td><strong>Nasal colonization</strong></td>
</tr>
<tr>
<td>Colonized with any Staphylococcus aureus</td>
</tr>
<tr>
<td>Colonized with MRSA</td>
</tr>
<tr>
<td><strong>Underwent cardiothoracic surgery</strong></td>
</tr>
<tr>
<td>Full median sternotomy</td>
</tr>
<tr>
<td>Any cardiothoracic procedure</td>
</tr>
<tr>
<td>CABG surgery only</td>
</tr>
<tr>
<td>Aortic valve</td>
</tr>
<tr>
<td>Mitral valve</td>
</tr>
<tr>
<td>Tricuspid valve</td>
</tr>
<tr>
<td>CABG surgery and valve</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass graft; IQR, interquartile range; MRSA, methicillin-resistant Staphylococcus aureus.

Additional data are expressed as No. (%) of participants unless otherwise indicated. Denominators were not adjusted for missing data. The 21 patients randomized at the site with questionable clinical practices (n=10 to the V710 group and n=11 to the placebo group) have been excluded from this table and all analyses.

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Immunogenicity

Preliminary characterization of the clinical isolates indicated that the isdB gene was highly conserved, with more than 95% homology. Anti-IsdB IgG titers at the time of surgery in V710 vaccine recipients were consistently greater than the prevaccination baseline levels, indicating that the vaccine was immunogenic (eFigure 3). Furthermore, the antibody titers after receipt of V710 vaccine were significantly higher than after receipt of placebo. Antibody responses in V710 recipients who developed primary S aureus infections were comparable with the titers achieved in V710 recipients who did not develop S aureus infection. Geometric mean anti-IsdB IgG levels peaked near postoperative day 45 and then slowly but steadily declined.

The V710 vaccine induced a significant, albeit modest and transient, increase in functional antibodies. The geometric mean increase in antibody titer with opsonophagocytic activity from baseline was 2.5-fold (95% CI, 1.2-2.8) in the subset of 299 V710 recipients evaluated 14 to 60 days after vaccination (just prior to surgery) and 1.9-fold (95% CI, 1.6-2.2) in the 94 V710 recipients evaluated at postoperative day 90, but had decreased to 1.2-fold (95% CI, 1.0-1.3) in the 84 V710 recipients evaluated on postoperative day 360. The corresponding percentages of evaluable V710 recipients achieving at least a 4-fold increase in opsonophago-

Table 2. Primary and Sensitivity Efficacy Analyses of the Composite Primary End Pointa

<table>
<thead>
<tr>
<th>Prespecified Analyses</th>
<th>V710 Vaccine Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary modified ITT analysis (vaccinated patients with staphylococcal infection, 5 deaths were attributed to multiorgan failure, all of which occurred in V710 recipients.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients With S aureus Bacteremia/Deep Sternal Wound Infection, No.</td>
<td>Follow-up, y(^b)</td>
</tr>
<tr>
<td>23</td>
<td>3815</td>
<td>903.6</td>
</tr>
<tr>
<td>Primary modified ITT analysis (vaccinated patients with full median sternotomy on postvaccination day 14-60)(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>3528</td>
<td>837.6</td>
</tr>
<tr>
<td>Supportive per-protocol analysis (vaccinated patients with full median sternotomy on postvaccination day 14-60 without major protocol violations)(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>3456</td>
<td>822.2</td>
</tr>
</tbody>
</table>

Abbreviations: ITT, intention-to-treat; S aureus, Staphylococcus aureus.

\(^a\) The prespecified primary end points were postoperative S aureus bacteremia and/or S aureus deep sternal wound infections through postoperative day 90.

\(^b\) Absolute rate of S aureus bacteremia or deep sternal wound infection per 100 person years = (c/years) \times 100, where c is the number of patients with S aureus bacteremia or deep sternal wound infection.

\(^c\) Vaccine efficacy was calculated as \(1 - (c_{V710}/c_{placebo}) \times 100\), where c is the number of patients with S aureus bacteremia or deep sternal wound infection, based on the number of cases in the V710 and placebo groups without regard to length of follow-up, as stipulated in the protocol and by regulatory agencies. To supplement the estimates of vaccine efficacy (which were based on the case split without regard to duration of follow-up), relative risks (which accounted for both the number of patients and length of follow-up time) were retrospectively computed for the key primary efficacy results. Because the length of follow-up was modestly different for the V710 and placebo groups, the relative risk reduction (1 - relative risk) closely approximates but does not exactly match the vaccine efficacy.

\(^d\) Patients experiencing a serious preoperative S aureus infection were to be excluded from these analyses. There were 2 such cases in each group, but none of these 4 patients developed a subsequent postoperative S aureus end point event during the study.
cystic antibody titer at these 3 points were 29% (95% CI, 24%-35%) at 14 to 60 days, 17% (95% CI, 10%-26%) at 90 days, and 4% (95% CI, 1%-10%) at 360 days. In contrast to the V710 group, the change in baseline geometric mean titer for evaluable placebo recipients was not significantly different from 1 (indicating no meaningful increase) at any of the 3 measurement points, and only 3 (1%; 95% CI, 0%-4%) of the 241 placebo recipients evaluated 14 to 60 days after vaccination had at least a 4-fold increase in titer.

### Table 3. Types and Frequencies of Adverse Experiences (AEs)

<table>
<thead>
<tr>
<th>No. of Events</th>
<th>V710 Vaccine Group (n = 3958)</th>
<th>Placebo Group (n = 3967)</th>
<th>Between-Group Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With any AE</td>
<td>1219 (30.8) [29.4-32.3]</td>
<td>866 (21.8) [20.6-23.1]</td>
<td>9.0 (7.0 to 10.9)</td>
</tr>
<tr>
<td>With vaccine-related AE&lt;sup&gt;b&lt;/sup&gt;</td>
<td>821 (20.7) [19.5-22.0]</td>
<td>437 (11.0) [10.1-12.0]</td>
<td>9.7 (8.1 to 11.3)</td>
</tr>
<tr>
<td>With febrile reaction&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17 (0.4) [0.3-0.7]</td>
<td>29 (0.7) [0.5-1.0]</td>
<td>ND</td>
</tr>
<tr>
<td>With vaccine-related febrile reaction AE&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>6 (0.2) [0.1-0.3]</td>
<td>13 (0.3) [0.2-0.6]</td>
<td>ND</td>
</tr>
<tr>
<td>With injection site AE&lt;sup&gt;c&lt;/sup&gt;</td>
<td>797 [20.1] [18.9-21.4]</td>
<td>378 [9.5] [8.6-10.5]</td>
<td>10.6 (9.1 to 12.2)</td>
</tr>
<tr>
<td>With vaccine-related injection site AE&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>760 [19.2] [18.0-20.5]</td>
<td>360 [9.1] [8.2-10.0]</td>
<td>10.1 (8.6 to 11.7)</td>
</tr>
<tr>
<td>With non-injection site AE</td>
<td>673 [17.0] [15.8-18.2]</td>
<td>602 [15.2] [14.1-16.3]</td>
<td>1.8 (0.2 to 3.4)</td>
</tr>
<tr>
<td>With vaccine-related non-injection site AE&lt;sup&gt;d&lt;/sup&gt;</td>
<td>122 (3.1) [2.6-3.7]</td>
<td>111 (2.8) [2.3-3.4]</td>
<td>0.3 (0.3 to 1.0)</td>
</tr>
<tr>
<td>With serious AE</td>
<td>66 [1.7] [1.3-2.1]</td>
<td>51 [1.3] [1.0-1.7]</td>
<td>0.4 (0.2 to 0.9)</td>
</tr>
<tr>
<td>With serious vaccine-related AE&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0 [0.0-0.1]</td>
<td>0 [0.0-0.1]</td>
<td>0.0 (0.1 to 0.1)</td>
</tr>
<tr>
<td>Who discontinued because of AE</td>
<td>0 [0.0-0.1]</td>
<td>0 [0.0-0.1]</td>
<td>0.0 (0.1 to 0.1)</td>
</tr>
<tr>
<td>Who died of any cause</td>
<td>11 [0.3] [0.1-0.5]</td>
<td>6 [0.2] [0.1-0.3]</td>
<td>0.1 (0.1 to 0.4)</td>
</tr>
</tbody>
</table>

Abbreviation: ND, not done because per the protocol statistical analysis plan, risk differences not computed when there was less than 1% observed adverse experiences in either group.<br><sup>a</sup>Differences (95% CIs) were calculated as the AE rate in the V710 group minus the AE rate in the placebo group, using the method of Miettinen and Nurminen.<br><sup>b</sup>Determined by investigator to be possibly, probably, or definitely vaccine-related.<br><sup>c</sup>Injection site and febrile reactions were actively solicited for the 5-day period immediately following vaccination. Oral temperatures<br><sup>d</sup>The follow-up time represents the number of days from vaccination to the date of either the first event (if the participant had an event) or the last day of study follow-up (if the participant did not have an event).<br><sup>e</sup>Associated with (although not necessarily caused by) S aureus infection.<br><sup>f</sup>Not prespecified per protocol but added after a safety signal was recognized during the second interim review. Nominal P value for the V710 group vs placebo group was P=.04.

### Table 4. Analysis of Mortality and Multiorgan Failure in Patients With Postoperative Staphylococcus aureus Infections

<table>
<thead>
<tr>
<th>No. of Events</th>
<th>V710 Vaccine Group (n = 3815)</th>
<th>Placebo Group (n = 3832)</th>
<th>Rate Difference, (95% CI) per 100 Person-Years&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with S aureus bacteremia or deep sternal wound infection</td>
<td>23 [11</td>
<td>28 8</td>
<td>28.0 (2.0-66.7)</td>
</tr>
<tr>
<td>Who died</td>
<td>7 4</td>
<td>19.6</td>
<td>35.7 (14.4-73.6)</td>
</tr>
<tr>
<td>Who died with multorgan failure</td>
<td>3 2</td>
<td>20.2</td>
<td>14.9 (3.1-43.4)</td>
</tr>
<tr>
<td>Patients with any S aureus infection</td>
<td>73 24</td>
<td>96 17</td>
<td>18.8 (8.0-34.1)</td>
</tr>
<tr>
<td>Who died</td>
<td>15&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8</td>
<td>65.2</td>
</tr>
<tr>
<td>Who died with multorgan failure</td>
<td>5</td>
<td>2</td>
<td>65.9</td>
</tr>
</tbody>
</table>

Abbreviation: MRSA, methicillin-resistant S aureus.<br><sup>a</sup>Follow-up time is the number of days from vaccination to the date of the first event (if the patient had an event) or the last day of study follow-up (if the patient did not have an event).<br><sup>b</sup>Estimated event rate = (total events/person-years) × 100.<br><sup>c</sup>The 1 additional V710 recipient with S aureus infection who died at the excluded site is not tabulated here. Inclusion of this patient would have yielded a mortality rate difference of 20.2 (9.2, 35.7) per 100 person-years.

### COMMENT

The development of a safe and effective vaccine against serious S aureus infections in high-risk populations would represent a major step forward, but continues to present unresolved challenges. Staphylococcus aureus vacc...
VACCINE TO PREVENT POSTSTERNOTOMY S AUREUS INFECTIONS

cine candidates to date have been
designed to elicit production of op-
sonic antibodies, but humoral immu-
nity may be inadequate to prevent S au-
reus infections.18-22 An earlier vaccine
containing S aureus types 5 and 8 cap-
sular polysaccharides conjugated to
nontoxic recombinant Pseudomonas ae-
ruginosa exotoxin A (StaphVAX, Nabi
Biopharmaceuticals) appeared to con-
ter limited short-term protection against
S aureus bacteremia in patients under-
going hemodialysis for approximately
40 weeks after vaccination in a proof-
of-concept study21; however, a larger
clinical trial later failed to demon-
strate any benefit.22

In our study of adult patients under-
going cardiothoracic surgery, preop-
erative vaccination with V710 did not
significantly reduce the composite in-
cidence of S aureus bacteremia and deep
sternal wound infection. Because vac-
cination with V710 resulted in consist-
tent humoral responses, the lack of ef-
cicacy was not simply due to failure to
boost IgG levels against homologous
IsdB. A numerical reduction in the
number of end points in the vaccine
group relative to the placebo group was
seen during the early postoperative pe-
riod when antibody titers were peak-
ing, but these differences were not sta-
tistically significant. In a series of post
hoc subgroup analyses uncorrected for
multiple comparisons, vaccine effici-
cacy was numerically higher against
MSSA than MRSA infections, superfi-
cial than deep surgical site infections,
and in baseline nasal S aureus carriers
than in noncarriers, but the wide con-
fidence intervals around these point es-
timates included zero. Overall mortal-
ity also did not significantly differ in the
2 groups. However, further analyses
demonstrated that S aureus–infected
V710 recipients were significantly more
likely to die postoperatively than S au-
reus–infected placebo recipients. A
higher mortality rate in infected V710
recipients relative to placebo recipients
was evident among patients experienc-
ing a primary end point (ie, bacteremia
and/or deep sternal wound infection) as
well as among patients developing any
type of postoperative S aureus infec-
tion.

In the second planned interim analy-
sis, multiorgan system failure in the
postoperative period (as gauged by se-
rious adverse event reporting) ap-
peared to be associated with receipt of
V710 vaccine. Since no protocol-
prescribed criteria for multiorgan fail-
ure were available, the adverse event
term could have been applied inconsis-
tently at different study sites. De-
spite the post hoc nature of the many
exploratory analyses, which were un-
adjusted for multiple comparisons, the
consistency of the association be-
 tween V710 and later development of
multiorgan failure across multiple sub-
groups raises the possibility that the re-
 lationship may not simply be the re-
sult of chance alone.

A causal relationship linking re-
ceipt of V710 vaccine to higher rates of
delayed multiorgan failure and mortal-
ity among S aureus–infected patients in
this trial has not been established.
MRSA infections, which have been as-
sociated with a higher mortality than
MSSA surgical site infections,23,24 were
more common in the V710 group than
the placebo group and potentially could
have contributed in part to the ob-
served higher mortality among V710 re-
cipients. However, a clear mechanism
by which the anti-IsdB antibody re-
sponse induced by preoperative re-
ceipt of V710 could have aggravated
the outcome of postoperative staphylococ-
il infections in our patients,25-27 de-
spite appearing safe and efficacious in
the early clinical studies and preclini-
 cal models,6-8 remains to be deter-
mined. The paradoxical finding of
worse outcomes after receipt of a vac-
cine has been previously en countered.

The role of humoral immunity in
protecting against S aureus is incom-
pletely understood.33 For example, the
presence of antibodies to the S aureus
Panton-Valentine leukocidin has been
associated with poor outcomes in a mu-
rine soft-tissue infection model.34 Op-
sonophagocytic antibodies induced by
V710 (if not accompanied by bacterial
killing) could theoretically permit in-
tracellular survival of S aureus,35 poten-
tially enhancing morbidity and mort-
tality; however, the increase in
opsonophagocytic activity observed af-
ter V710 administration was generally
modest. Subsequent to termination of
our study, the potential role of cell-
mediated immunity in protection
against S aureus infections has re-
ceived increasing attention.18,19,36

In conclusion, the use of the V710
vaccine against S aureus did not
reduce the rate of serious postopera-
tive S aureus infections compared
with placebo and was associated with
increased mortality among patients
who developed S aureus infections.
These findings do not support the
use of the V710 vaccine for patients
undergoing surgical interventions.

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